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# Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever) (Review)

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[Intervention Review]

# Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever)

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## ABSTRACT

### Background

**Review status:** Current question - no update intended. Azithromycin treatments are included in the review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever). (Thaver D, Zaidi AKM, Critchley JA, Azmatullah A, Madni SA, Bhutta ZA. Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever). Cochrane Database of Systematic Reviews 2008, Issue 4. Art. No.: CD004530. DOI: 10.1002/14651858.CD004530.pub3.) This latter review is being updated, and will be published in late 2011.

Enteric fever (typhoid and paratyphoid fever) is potentially fatal. Infection with drug-resistant strains of the causative organism *Salmonella enterica* serovar Typhi or Paratyphi increases morbidity and mortality. Azithromycin may have better outcomes in people with uncomplicated forms of the disease.

### Objectives

To compare azithromycin with other antibiotics for treating uncomplicated enteric fever.

### Search methods

In August 2008, we searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (*The Cochrane Library* 2008, Issue 3), MEDLINE, EMBASE, LILACS, and *m*RCT. We also searched conference proceedings, reference lists, and contacted researchers and a pharmaceutical company.

### Selection criteria

Randomized controlled trials comparing azithromycin with other antibiotics for treating children and adults with uncomplicated enteric fever confirmed by cultures of *S.* Typhi or Paratyphi in blood and/or stool.

### Data collection and analysis

Both authors independently extracted data and assessed the risk of bias. Dichotomous data were presented and compared using the odds ratio, and continuous data were reported as arithmetic means with standard deviations and were combined using the mean difference (MD). Both were presented with 95% confidence intervals (CI).

**Main results**

Seven trials involving 773 participants met the inclusion criteria. The trials used adequate methods to generate the allocation sequence and conceal allocation, and were open label. Three trials exclusively included adults, two included children, and two included both adults and children; all were hospital inpatients. One trial evaluated azithromycin against chloramphenicol and did not demonstrate a difference for any outcome (77 participants, 1 trial). When compared with fluoroquinolones in four trials, azithromycin significantly reduced clinical failure (OR 0.48, 95% CI 0.26 to 0.89; 564 participants, 4 trials) and duration of hospital stay (MD -1.04 days, 95% CI -1.73 to -0.34 days; 213 participants, 2 trials); all four trials included people with multiple-drug-resistant or nalidixic acid-resistant strains of *S.* Typhi or *S.* Paratyphi. We detected no statistically significant difference in the other outcomes. Compared with ceftriaxone, azithromycin significantly reduced relapse (OR 0.09, 95% CI 0.01 to 0.70; 132 participants, 2 trials) and not other outcome measures. Few adverse events were reported, and most were mild and self limiting.

**Authors' conclusions**

Azithromycin appears better than fluoroquinolone drugs in populations that included participants with drug-resistant strains. Azithromycin may perform better than ceftriaxone.

# PLAIN LANGUAGE SUMMARY

**Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever)**

Typhoid or paratyphoid fevers (known as enteric fever) are infectious diseases caused by *Salmonella* bacteria. There were over 25 million new cases worldwide in 2000. Infections are mostly in the middle- and low-income countries where sanitation and water supplies are poor. The diseases are common in the Indian subcontinent, South-East and Far East Asia, Africa, Central and South America, and the Mediterranean region. Enteric fever occurs mainly in young people between five and 19 years and in some areas it is common among children less than five years' old. The infection is usually transmitted by ingestion of food or water contaminated with faeces from people who have the infection. Symptoms include intermittent fever, severe headaches, abdominal discomfort, loss of appetite, malaise, vague abdominal tenderness, and enlarged liver and/or spleen. About 10% to 15% of people get complications, which include bleeding, shock, and inflammation of the pancreas, heart muscles, and the brain. For many years, antibiotics such as chloramphenicol, ampicillin, and cotrimoxazole were used for treating enteric fever. However, multiple-drug resistant strains of the bacteria have now emerged. Other antibiotics like the fluoroquinolones, cephalosporins, and azithromycin are used as well. This review of trials looked at azithromycin as a treatment for uncomplicated enteric fever. There were seven trials (from Egypt, Vietman, and India) involving 773 people, all treated in hospital. There was limited evidence showing azithromycin is effective for treating typhoid or paratyphoid fevers. This is especially important where there are multiple-drug resistant strains. Azithromycin was better than some of the other drugs used. However, care will need to be taken to prevent strains becoming resistant to azithromycin too. More large trials, preferably multicentred and involving outpatients in areas endemic for enteric fever, are needed.

# BACKGROUND

## Definition

Enteric fever (typhoid or paratyphoid fever) is a potentially fatal systemic infection. Typhoid fever is caused by *Salmonella enterica* serovar Typhi (*S.* Typhi) and paratyphoid fever is caused by *Salmonella enterica* serovar Paratyphi (*S.* Paratyphi) *A*, *B*, or*C*. These organisms cause disease specifically in humans. Paratyphoid fever is usually a less serious infection with milder symptoms and causes fewer deaths (Maskalyk 2003), although it may occasionally become complicated (Lang 1992; Rajagopal 2002).

## Epidemiology

An estimated 21.6 million new cases of typhoid fever with about 216,510 deaths occurred globally in 2000. Paratyphoid fever caused about 5.4 million illnesses in the same year (Crump 2004).

Most cases occur in the middle-income and low-income countries where sanitation is poor and water supply is inadequate (Lesser 2001). Endemic enteric fever is common in the Indian subcontinent, South-East and Far East Asia, Africa, Central and South America, and the Mediterranean region (Corales 2000). Incidence rates vary across areas; for instance, annual incidence rates of 198 per 100,000 have been reported in the Mekong valley region of Vietnam (Lin 2002) and 980 per 100,000 in Delhi, India (Sinha 1999). In the USA, most infections are linked to international travel to countries where the disease is endemic; 356 cases were reported in 2003 (Hopkins 2005).

The peak incidence occurs in people between five and 19 years, and young adults (Bhan 2005). However, in some areas it is common among children less than five years' old (Sinha 1999). There are several risk factors for the infection such as extremes of age, sickle cell anaemia, a lack of acid in gastric juice (as seen in the elderly), and gastric surgery (Parry 1984; Corales 2000). The mortality rate is about 10% to 15% if untreated and is highest among children aged less than one year and the elderly (Butler 1991; Bhutta 1996).

### Pathogenesis

The infection is usually transmitted by ingestion of food or water contaminated with faeces from people who have an acute infection, are convalescing, or are chronic carriers. A chronic carrier is defined as someone who excretes *S.* Typhi in stool or urine for more than one year (Bhan 2005). The severity of the infection is dependent on the initial infective dose, virulence of the organism, and the host immune response (Adams 1987). The organisms usually penetrate the intestinal lining from where they multiply in lymphoid tissues, are released into the blood stream, and then spread to various body organs, most commonly the liver, spleen, bone marrow, and gall bladder (Lesser 2001).

### Clinical features

The clinical features of uncomplicated enteric fever include progressive intermittent fever, severe headaches, abdominal discomfort, cough, loss of appetite, malaise, vague abdominal tenderness, enlarged liver and/or spleen, and in the fair-skinned, rose-coloured spots on the chest and abdomen (Lesser 2001). Complications may include intestinal perforation that may require surgery, intestinal bleeding needing blood transfusion, shock, pancreatitis (inflammation of the pancreas), pneumonia, myocarditis (inflammation of the heart muscles), meningitis (inflammation of the covering of the brain), and psychosis (altered mental state). They occur in 10% to 15% of people and commonly in those people whose illness has lasted more than two weeks (Parry 2002), and usually require admission into hospital.

### Diagnosis

The definitive diagnosis of enteric fever is the isolation of the organisms from blood or bone marrow. Cultures of bone marrow aspirate are reported to be positive in about 60% to 90% of patients, and organisms can be cultured even when patients have had antibiotics for some days (Vallenas 1985; Akoh 1991; Gasem 1995; Corales 2000). Stool, urine, intestinal secretions, rectal swabs, and skin snips of rose spots can also be cultured, but these have low yields. Serologic tests, like the agglutination reaction (Widal reaction), are not reliable because of false-positive results owing to cross-reaction with other *Salmonella* spp. and a sensitivity of only 70% (Maskalyk 2003). Newer methods of diagnosis such as the use of DNA probes and polymerase chain reaction to detect *S. Typhi* directly in blood are now available, but their use in endemic areas is limited (Parry 2002).

### Treatment and drug resistance

For many decades, antibiotics such as chloramphenicol, ampicillin, and cotrimoxazole were used for treating enteric fever (Lesser 2001). The emergence of multiple-drug-resistant (MDR) *Salmonella* strains, which are resistant to chloramphenicol, ampicillin, and cotrimoxazole, has changed treatment options. MDR strains of *S.* Typhi have been reported from all parts of the world. In Quetta, Pakistan for instance 69% of *S.* Typhi isolated from blood was MDR (Mirza 1996), whereas in Vietnam 89.9% of isolates between 1998 and 2002 were MDR (Le 2004). Resistance was considerably lower in Tajikistan where 27% of isolates were MDR (Mermin 1999). A cluster of six cases with MDR typhoid has also been reported in South Africa (Coovadia 1992). In Nigeria and Kenya, MDR typhoid is reported as 61% (Akinyemi 2005) and 82.4% (Kariuki 2004) respectively. In 1995, 28% of all isolates of *S.* Typhi from humans in the USA were resistant to a wide range of drugs including ampicillin, chloramphenicol, streptomycin, sulphonamides, and tetracyclines (Ribot 2002). The incidence of MDR *S.* Typhi in the UK was reported as over 50% in 1999, up from 34% in 1995 and 1.5% six years earlier (Rowe 1997; Threlfall 2001). However, there are recent reports from Egypt and the Indian subcontinent of a fall in the proportion of MDR strains of *S.* Typhi (Wasfy 2002; Madhulika 2004; Lakshmi 2006).

Second-line antibiotics like the fluoroquinolones (ciprofloxacin, ofloxacin, perfloxacin), third-generation cephalosporins (ceftriaxone, cefotaxime, cefixime), and azithromycin are often now used for treating MDR typhoid fever. (See Thaver 2008 for a Cochrane Review of fluoroquinolones for treating enteric fever.) Infections with isolates susceptible to nalidixic acid (prototype fluoroquinolone) respond extremely well to fluoroquinolones. Lately, there have been several reports of fluoroquinolone-resistant *S.* Typhi (Murdoch 1998; Asna 2003; Butt 2003). However, there are problems with identifying these strains. *S.* Typhi resistant to nalidixic acid may not respond to ciprofloxacin despite having minimum inhibitory concentration (MIC) values within current Clinical and Laboratory Standards Institute (CLSI) susceptibility range for ciprofloxacin (Wain 1997; Threlfall 1999; Ackers 2000). This means that in vitro susceptibility may not always translate to in vivo efficacy and that there is risk of treatment failures in those infected with such strains (Aarestrup 2003; Crump 2003). Nalidixic acid-resistant (NaR) isolates of *S.* Typhi and *S.* Paratyphi A are defined as susceptible by the microbiology laboratory using the current CLSI breakpoints; however, they have reduced susceptibility to fluoroquinolones compared with wild-type strains and also respond less well to fluoroquinolone therapy. These are distinct from isolates of *S.* Typhi and Paratyphi A that are fully resistant to fluoroquinolones, for which treatment with fluoroquinolones will always lead to failure. Essentially there are three categories of susceptibilities to fluoroquinolones: fully susceptible (ie susceptible to nalidixic acid and ciprofloxacin); reduced susceptibility (ie NaR and susceptible to ciprofloxacin); and resistant (NaR and ciprofloxacin) (Rupali 2004; Parry 2006; Kownhar 2007).

Quinolone-resistant strains are reportedly also MDR (Parry 2002), and infection with resistant *S.* Typhi is associated with increased morbidity and mortality (Coovadia 1992). There are also reports from the Indian subcontinent of isolates that are fully resistant to fluoroquinolones and the extended spectrum cephalosporins (Renuka 2005; Mushtaq 2006; Joshi 2007). These reports further support the need for alternative antibiotics such as azithromycin for treating drug-resistant enteric fever.

## Azithromycin

Azithromycin, a member of the macrolide group of antibiotics, has been used as an alternative drug for treating typhoid fever. It achieves low intravascular levels, has high intracellular tissue penetration, and a long elimination half life of 72 hours. These properties make for once-daily administration and reduction in the duration of therapy. The drug is rapidly absorbed from the gut and is well-tolerated when used orally (Carbon 1998; Chambers 2004). Adverse effects include allergic reactions, liver damage, nausea, diarrhoea, abdominal pains, rashes, and arrhythmias. In vitro studies have shown that it is more potent than traditional first-line drugs and other macrolides against *Salmonella* spp. with an average MIC of 8 $\mu$g/mL (range 4 to 16 $\mu$g/mL) (Metchock 1990; Butler 2001). There are no reports of resistance of *S.* Typhi to azithromycin, and recent studies have shown that it is effective both clinically and bacteriologically in treating enteric fever even in those caused by MDR strains (Tribble 1995; Girgis 1999). However, it is important to note that there are no currently accepted breakpoints and disc susceptibility zone interpretative criteria for azithromycin against *Salmonella* spp. Thus, it is difficult for laboratories to categorically state that a *S.* Typhi or *S.* Paratyphi isolate is susceptible or resistant to the drug.

This review therefore aims to assess available evidence on the efficacy and safety of azithromycin as an alternative drug in treating uncomplicated enteric fever.

# OBJECTIVES

To compare azithromycin with other antibiotics for treating uncomplicated enteric fever.

# METHODS

## Criteria for considering studies for this review

### Types of studies

Randomized controlled trials.

### Types of participants

Children or adults with uncomplicated enteric fever confirmed by culture of *S.* Typhi or *S.* Paratyphi in blood, stool, urine, or bone marrow aspirate. We define uncomplicated enteric fever as clinical diagnosis of typhoid or paratyphoid fever without overwhelming toxaemia, intestinal haemorrhage, intestinal perforation, shock, psychosis, or convulsions at the start of treatment.

### Types of interventions

#### Intervention

Oral azithromycin.

#### Control

Other antibiotics such as chloramphenicol, ampicillin, amoxicillin, cotrimoxazole, ceftriaxone, and any fluoroquinolone.

### Types of outcome measures

#### Primary

- Clinical failure, defined as persistent symptoms or development of complications requiring prolonged treatment or the addition or change of antimicrobial agent.
- Microbiological failure, defined as a positive culture from blood, bone marrow, or stool at the end of treatment as defined by trial authors.

#### Secondary

- Fever clearance time, defined as time in hours from start of trial or control drug until body temperature falls to values less than 38 °C and remains so for a period as specified by trial authors.
- Duration of hospital stay, defined as time in days from entry into trial until discharge.
- Relapse, defined as recurrence of symptoms in addition to a positive culture from blood, bone marrow, or stool within 30 days during the follow-up period.

#### Adverse events

- Serious adverse events, defined as those leading to death (eg intestinal perforation and haemorrhage), prolonged hospitalization (eg cholestatic jaundice), and disability.
- Adverse events requiring discontinuation of treatment (eg markedly elevated liver enzymes and impaired renal function).
- Other adverse events (eg nausea, vomiting, and diarrhoea).

## Search methods for identification of studies

We attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

We searched the following databases using the search terms and strategy described in Table 1: Cochrane Infectious Diseases Group Specialized Register (August 2008); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (2008, Issue 3); MEDLINE (1966 to August 2008); EMBASE (1974 to August 2008); and LILACS (1982 to August 2008). We also searched the *meta*Register of Controlled Trials (*m*RCT) in August 2008 using 'azithromycin' and 'typhoid' as search terms.

We searched the conference proceedings of the $5^{th}$ International Symposium on Typhoid Fever and other Salmonellosis, Karachi, Pakistan, 4 to 7 February 2002 for relevant abstracts. We contacted experts in the field, Drs Christopher Parry and Jeremy Farrar, for unpublished and/or ongoing trials. We also checked the reference lists of all studies identified by these methods.

## Data collection and analysis

### Selection of studies

Both authors independently screened results of literature search for potentially relevant trials. We retrieved full reports of the identified trials and independently determined if they met the inclusion criteria using a pre-tested eligibility form. We resolved contentious issues by discussion and, where necessary, by consulting a Cochrane Infectious Diseases Group (CIDG) Editor. We also attempted to contact authors for further information if trial eligibility was unclear. We listed all excluded studies along with the reasons for exclusion in the 'Characteristics of excluded studies'. We ensured that trials with multiple publications were included only once.

### Data extraction and management

Both authors independently extracted data analysed as stated in the trial protocol using a pre-tested data extraction form. We extracted data for dichotomous outcomes, such as clinical failure and microbiological failure, by recording the total number of participants randomized, those that experienced these outcomes, and the number analysed. For continuous outcomes, such as fever clearance time and duration of hospital stay, we extracted the total number of participants analysed, arithmetic means, and standard deviation. Where standard deviations were not reported, we derived them using standard error of the mean. We also extracted data on reported adverse events. We contacted trial authors where the relevant details were not recorded or were unclear. Contentious issues were resolved by consensus or, when necessary, by consulting a CIDG Editor. The first author entered the data into Review Manager 5.

### Assessment of risk of bias in included studies

Both authors independently assessed the risk of bias of eligible trials using a specially designed pre-tested form. We assessed generation of allocation sequence and allocation concealment as adequate, inadequate, or unclear according to Jüni 2001. We reported which parties (participant, care provider, or assessor) were blinded in each trial. We considered inclusion of all randomized culture-positive participants in the analysis to be adequate if 90% or more were included, inadequate if less than 90%, and unclear if this was not stated. We resolved disagreements through discussion or by consulting a CIDG Editor. We attempted to contact the trial authors where the method was either not stated or unclear.

### Data synthesis

We analysed data using Review Manager 5. All results were presented with 95% confidence intervals (CI). Dichotomous data were presented and compared using the odds ratio. Continuous data, where arithmetic means and standard deviations (SD) were reported, were combined using the mean difference (MD). Where arithmetic means were reported for an outcome and the scale was naturally bound at zero, the ratio of the mean to standard deviation was used to check the assumption that the data were normally distributed. If we suspected the data were skewed (mean/SD < 2), then we did not combine the data in a meta-analysis.

### Subgroup analysis and investigation of heterogeneity

We assessed heterogeneity amongst the trials by inspecting the forest plot and using the chi-squared test (with P value < 0.1 representing heterogeneity) and the $I^2$ test (50% represents moderate level of heterogeneity). When we detected any heterogeneity among the trials for any outcome, we combined them using the random-effects model. We planned to do subgroup analyses for participant age (child versus adult), hospitalization (hospitalized or not), presence of multiple-drug resistance, and duration of treatment, but this was not possible as there were few trials with limited numbers of participants.

### Sensitivity analysis

We could not conduct sensitivity analyses to explore the effect of the trials' risk of bias assessment, particularly allocation concealment, on the results. This was because there were few trials in each comparison. For the same reason publication bias could not be assessed using the funnel plot.

# RESULTS

## Description of studies

### Trial selection

Eleven trials were identified and assessed for eligibility. Seven trials involving 773 participants met the inclusion criteria (Butler 1999; Girgis 1999; Chinh 2000; Frenck 2000; Frenck 2004; Parry 2007; Dolecek 2008); see details in the 'Characteristics of included studies'. Four were excluded (Wallace 1994; Tribble 1995; Chiu 1999; Li 2005); see details in the 'Characteristics of excluded studies'. One ongoing study was also identified and is described in the 'Characteristics of ongoing studies' (ISRCTN66534807).

### Trial design and location

Three trials were conducted in Egypt (Girgis 1999; Frenck 2000; Frenck 2004), three in Vietnam (Chinh 2000; Parry 2007; Dolecek 2008), and one in India (Butler 1999). Both Butler 1999 and Dolecek 2008 were multicentred.

### Participants

Three trials included only adults with the minimum reported age of 15 years (Butler 1999; Girgis 1999; Chinh 2000). Two trials were exclusively in children and adolescents with a minimum age of three years and a maximum of 17 years (Frenck 2000; Frenck 2004). Two trials had both children and adult participants with an age range of one to 42 years (Parry 2007; Dolecek 2008). All the trials were conducted on inpatients who had uncomplicated enteric fever and were found to have positive blood and/or stool cultures for *S.* Typhi or *S.* Paratyphi. All the trials had participants with MDR strains of *S.* Typhi. In two trials, Chinh 2000 and Dolecek 2008, over half of the participants were infected with MDR *S.* Typhi, while in another, Parry 2007, more than 80% of isolates were MDR. Nearly 100% had NaR *S.* Typhi in Parry 2007 and Dolecek 2008.

### Inclusion and exclusion criteria

All included trials reported well-defined inclusion and exclusion criteria. Criteria for enrolment were clinical but positive blood/or stool culture for *S.* Typhi or *S.* Paratyphi required for inclusion in the study. All trials excluded pregnant and lactating women, and those with serious underlying diseases, previous antibiotic treatment, severe illness, and history of allergy to any of the study drugs.

### Interventions

Trials compared azithromycin with ceftriaxone (Frenck 2000; Frenck 2004), ciprofloxacin (Girgis 1999), ofloxacin (Chinh 2000; Parry 2007), gatifloxacin (Dolecek 2008), and chloramphenicol (Butler 1999). No trials compared azithromycin with other first-line antibiotics such as ampicillin and cotrimoxazole.
All seven trials used a short-course azithromycin regimen (five to seven days). Two trials treated participants for five days (Chinh 2000; Frenck 2004), whereas the other five trials used a seven-day regimen (Butler 1999; Girgis 1999; Frenck 2000; Parry 2007; Dolecek 2008).

### Outcome measures

#### Primary outcomes

Definitions and time points at which primary outcomes were measured varied. Some trials considered response as 'clinical cure' or 'microbiological cure'. In two trials, microbiological failure was not explicitly defined (Butler 1999; Frenck 2000) and, in two other trials, the definition of fever clearance was unclear (Frenck 2000; Frenck 2004); see details in Table 2. We were able to extract data on both primary outcomes (clinical failure and microbiological failure) from all seven trials.

#### Secondary outcomes

We were able to extract data on all three secondary outcomes (fever clearance time, relapse, and duration of hospital stay) from only two trials (Chinh 2000; Parry 2007). Apart from Frenck 2000

and Frenck 2004, the other three trials did not include data on duration of hospital stay.
We could extract data on adverse events (both clinical and laboratory) from four trials (Girgis 1999; Chinh 2000; Frenck 2004; Dolecek 2008). One trial only reported laboratory-based adverse events (Frenck 2000), while one reported only clinical adverse events (Butler 1999).

#### MDR and NaR strains

All seven trials reported the proportion of participants with MDR strains. One trial did not specify the proportion in either study arm (Butler 1999), and only three trials indicated the proportion of participants with NaR strains in either study arm study (Chinh 2000; Parry 2007; Dolecek 2008,). Overall, between 1.5% and 85% of participants were infected with MDR strains especially of *S.* Typhi; see Table 3 for details.

## Risk of bias in included studies

See Table 4 for a summary of the risk of bias assessment.

### Generation of allocation sequence

All seven included trials used an adequate method to generate the allocation sequence: random-number list (Frenck 2000; Girgis 1999); table of random numbers (Butler 1999); random-number generator (Frenck 2004); and computer-generated randomization list (Chinh 2000; Parry 2007; Dolecek 2008).

### Allocation concealment

All included trials used an adequate method to conceal allocation (sealed envelopes).

### Blinding

Six trials were described as open for participants and physicians/caregivers (Butler 1999; Girgis 1999; Chinh 2000; Frenck 2000; Frenck 2004; Parry 2007). Dolecek 2008 was described simply as open label. One trial specifically stated that outcome assessors were not blinded (Butler 1999), while we obtained similar information from the trialists of two other trials (Chinh 2000; Parry 2007). The blinding of outcome assessors was unclear in three trials (Girgis 1999; Frenck 2000; Frenck 2004).

### Inclusion of all culture-positive participants in final analysis

In all seven trials, only culture-positive participants were considered evaluable. Six trials included 90% or more of culture-positive participants in the final analysis, while Butler 1999 included 84%.

### Intention-to-treat analyses

In all but Dolecek 2008 the trialists' analyses of the results were not by intention to treat as they excluded culture-negative participants. The analyses were both as pre-specified in the protocol (per protocol) and by intention to treat in Dolecek 2008; we used the per protocol data in this review.

## Effects of interventions

### 1. Azithromycin versus chloramphenicol

#### Clinical and microbiological failure

One trial with 77 participants, including 11% with MDR *S.* Typhi, made this comparison (Butler 1999). There was a tendency for azithromycin to have lower odds of clinical failure, but the results were not statistically significant (77 participants, Analysis 1.1). There was also no statistically significant difference in the odds of microbiological failure in both groups (77 participants, Analysis 1.2).

#### Relapse

No relapses were reported.

#### Fever clearance time

Fever clearance time was shorter in the azithromycin group (mean 98.4 hours) compared to the chloramphenicol group (mean 103.2 hours), but the results were not statistically significant (77 participants, Analysis 1.3).

#### Duration of hospital stay

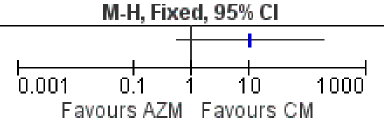
No data were reported for duration of hospital stay.

#### Adverse events

No data were reported for serious adverse events (Table 5). Five other adverse events were reported in the azithromycin group ( Table 6), two were gastrointestinal (no details for the other three). No other adverse events were reported for the chloramphenicol group (77 participants, Figure 1, Analysis 1.4).

**Figure 1. Azithromycin (AZM) vs chloramphenicol (CM): Adverse events (excluding serious adverse events)**

| | AZM | | CM | | Odds Ratio | Odds Ratio |
|---|---|---|---|---|---|---|
| Study or Subgroup | Events | Total | Events | Total | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Butler 1999 | 5 | 42 | 0 | 35 | 10.41 [0.56, 195.25] | |




## 2. Azithromycin versus fluoroquinolones

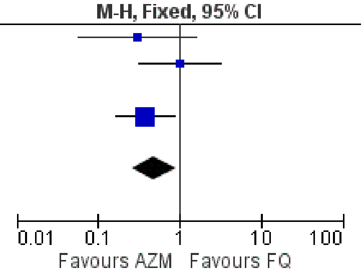
Four trials involving 564 participants compared azithromycin with ciprofloxacin (Girgis 1999, 64 participants), ofloxacin (Chinh 2000, 88 participants and Parry 2007, 125 participants), and gatifloxacin (Dolecek 2008, 287 participants). The trials had varying proportions of participants with MDR and NaR strains. In Girgis 1999, a third of participants were infected with MDR strains, with 16.6% of participants in the azithromycin group and 53.6% in the ciprofloxacin group. Over half (77%) of participants in Chinh 2000 had MDR strains of *S.* Typhi: 48.5% were in the azithromycin group and 51.5% were in the ofloxacin group. Also, 46 (52%) participants were infected with NaR strains, 25 in the azithromycin group and 21 in the fluoroquinolone group. Of the participants in Parry 2007, 85% and 89% of those in the azithromycin group were infected with MDR and NaR strains, respectively, compared to 90% and 98% respectively in the ofloxacin group. In Dolecek 2008, 58% of the isolates were reported as MDR (87 in the gatifloxacin arm and 66 in the azithromycin), while 96% were NaR (132 in the gatifloxcin arm and 121 in the azithromycin arm).

### Clinical and microbiological failure

There were fewer clinical failures with azithromycin (OR 0.48, 95% CI 0.26 to 0.89; 564 participants, 4 trials, Figure 2, Analysis 2.1). There were no statistically significant differences in microbiological failure (564 participants, 4 trials, Analysis 2.2) and relapse (491 participants, 4 trials, Analysis 2.3).

**Figure 2. Azithromycin (AZM) vs fluoroquinolones (FQ): Clinical failure**

| | AZM | | FQ | | | Odds Ratio | Odds Ratio |
|---|---|---|---|---|---|---|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Chinh 2000 | 2 | 44 | 6 | 44 | 19.0% | 0.30 [0.06, 1.59] | |
| Dolecek 2008 | 6 | 142 | 6 | 145 | 18.8% | 1.02 [0.32, 3.25] | |
| Girgis 1999 | 0 | 36 | 0 | 28 | | Not estimable | |
| Parry 2007 | 11 | 62 | 23 | 63 | 62.2% | 0.38 [0.16, 0.86] | |
| **Total (95% CI)** | | **284** | | **280** | **100.0%** | **0.48 [0.26, 0.89]** | |
| Total events | 19 | | 35 | | | | |
| Heterogeneity: Chi² = 2.28, df = 2 (P = 0.32); I² = 12% | | | | | | | |
| Test for overall effect: Z = 2.33 (P = 0.02) | | | | | | | |



### Relapse

There were no statistically significant differences in relapse (491 participants, 4 trials, Analysis 2.3).

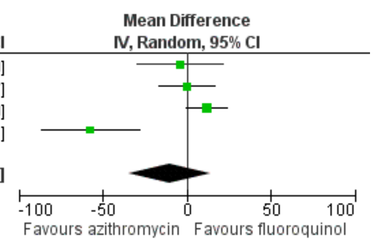
### Fever clearance time

There was marked heterogeneity for fever clearance time with no significant difference between the interventions when analysed using the random-effects model (564 participants, 4 trials, Figure 3, Analysis 2.4). The heterogeneity may be explained by differences in the definition of fever clearance time and the different fluoroquinolones used in the four trials.

**Figure 3. Azithromycin (AZM) vs fluoroquinolones (FQ): Fever clearance time (h)**

| | AZM | | | FQ | | | | Mean Difference |
|---|---|---|---|---|---|---|---|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI |
| Chinh 2000 | 130 | 40.61 | 44 | 134 | 76.14 | 44 | 23.1% | -4.00 [-29.50, 21.50] |
| Dolecek 2008 | 106 | 72.96 | 142 | 106 | 73.73 | 145 | 26.9% | 0.00 [-16.97, 16.97] |
| Girgis 1999 | 91.2 | 26.4 | 36 | 79.2 | 24 | 28 | 28.6% | 12.00 [-0.39, 24.39] |
| Parry 2007 | 139.2 | 67.49 | 62 | 196.8 | 97.18 | 63 | 21.4% | -57.60 [-86.89, -28.31] |
| **Total (95% CI)** | | | **284** | | | **280** | **100.0%** | **-9.80 [-34.15, 14.56]** |

Heterogeneity: Tau² = 499.39; Chi² = 18.55, df = 3 (P = 0.0003); I² = 84%
Test for overall effect: Z = 0.79 (P = 0.43)



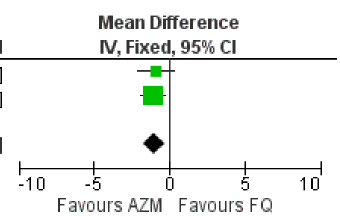

### Duration of hospital stay

Two trials reported on the duration of hospital stay (Chinh 2000; Parry 2007), which was significantly shorter in the azithromycin group (MD -1.04 days, 95% CI -1.73 to -0.34 days; 213 participants, 2 trials, Figure 4, Analysis 2.5).

**Figure 4. Azithromycin (AZM) vs fluoroquinolones (FQ): Duration of hospital stay (days)**

| | AZM | | | FQ | | | | Mean Difference |
|---|---|---|---|---|---|---|---|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% CI |
| Chinh 2000 | 9.6 | 2.37 | 44 | 10.5 | 3.38 | 44 | 32.4% | -0.90 [-2.12, 0.32] |
| Parry 2007 | 12.6 | 2.2 | 62 | 13.7 | 2.6 | 63 | 67.6% | -1.10 [-1.94, -0.26] |
| **Total (95% CI)** | | | **106** | | | **107** | **100.0%** | **-1.04 [-1.73, -0.34]** |

Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%
Test for overall effect: Z = 2.92 (P = 0.003)




### Adverse events

There were no serious adverse events reported in any of the trials (see Table 5). Adverse events that lead to discontinuation of the trial drugs included gastrointestinal bleeding in four participants and maculopapular rash in a participant. Both events were in the azithromycin arm of Dolecek 2008. There was a single event of gastrointestinal bleeding in each arm of Chinh 2000, but the trial drugs were not discontinued (Table 6).

Other common clinical adverse events reported in both arms of all included trials were nausea, vomiting, abdominal pains and skin rash. In Dolecek 2008, two participants in the azithromycin arm developed features of liver dysfunction and another two had pneumonia. One participant in each of the azithromycin and ofloxacin groups reported joint discomfort in Parry 2007. Laboratory-based adverse events were thrombocytosis and elevated aspartate amino transaminases, but these were not different between treatment groups.

### 3. Azithromycin versus ceftriaxone

Two trials involving 132 children made this comparison (Frenck 2000; Frenck 2004). About 17% of participants had *S.* Typhi MDR strains in Frenck 2000, whereas Frenck 2004 reported only one participant with MDR strains.

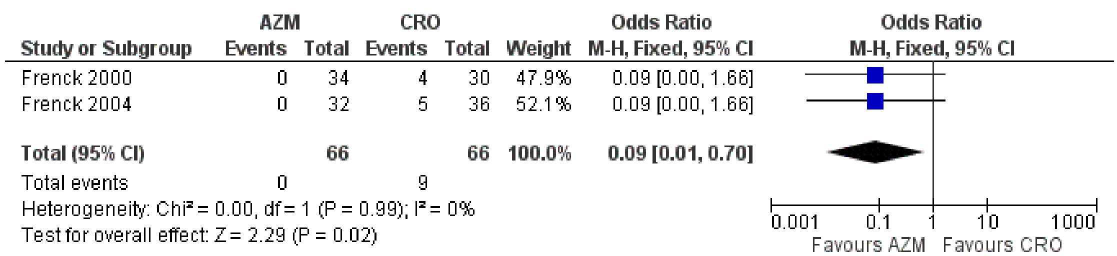
#### Clinical and microbiological failure

There was no statistically significant difference between the two groups in the odds of clinical failure (132 participants, 2 trials, Analysis 3.1) and microbiological failure (132 participants, 2 trials, Analysis 3.2).

#### Relapse

The odds of relapse were reduced by 91% in the azithromycin group and this was statistically significant, but the number analysed is small and the confidence intervals wide (OR 0.09, 95% CI 0.01 to 0.70; 132 participants, 2 trials, Figure 5, Analysis 3.3).

**Figure 5. Azithromycin (AZM) vs ceftriaxone (CRO): Relapse**




#### Fever clearance time

Fever clearance time was less in the ceftriaxone arm, but the difference was not statistically significant (132 participants, 2 trials, Analysis 3.4).

#### Duration of hospital stay

Neither trial reported on duration of hospitalization.

#### Adverse events

There were no reported serious adverse events (Table 5). Both trials reported gastrointestinal symptoms as common with vomiting commonest in the azithromycin group in Frenck 2000. Pain at the injection site was reported in six participants in the ceftriaxone group. Other adverse events included mild increases in aspartate and alanine transaminases, and thrombocytosis in both groups.

## DISCUSSION

Seven trials met our inclusion criteria and all were conducted in low- and middle-income countries. These areas have a high burden of the disease and present greater opportunities for disease transmission, including transmission of antibiotic-resistant *S. enterica* strains. Enteric fever caused by MDR and NaR strains is a significant public health problem as it appears to be responsible for outbreaks of epidemics in these areas (Parry 2004).

The methodological quality of all seven included trials was generally high. For instance, all trials used adequate methods to generate the allocation sequence and conceal allocation. The trials included adults, children, or both, and all participants were given a definitive diagnosis through the isolation of *S.* Typhi or *S.* Paratyphi from blood and/or stools. The choice of microbiologic cultures over serologic diagnosis may be because the clinical manifestation of the disease may be atypical in children and adults, and a distinction from other febrile illnesses is difficult to make in some adults (Ferreccio 1984; Dutta 2001; Bhan 2005). However, serologic diagnosis with the Widal or other serological tests is widely used in endemic areas as facilities for microbiologic cultures are lacking (House 2001). Few trials reported the proportion of participants infected with MDR or NaR strains. Only three of the trials indicated the proportion of NaR strains in the trial arms (Chinh 2000; Parry 2007; Dolecek 2008), although reports of such strains date back over a decade ago and are found in virtually all continents. The proportion of participants with NaR strains is particularly important for the comparison with fluoroquinolones because such strains may exhibit reduced susceptibility to fluoroquinolones. Chinh 2000, Parry 2007, and Dolecek 2008 were three of the four trials comparing azithromycin with fluoroquinolones, and both involved a high proportion of NaR infections. However, the NaR infections did not significantly affect the outcomes for both intervention drugs.

The included trials compared azithromycin with chloramphenicol (Butler 1999), fluoroquinolones (ciprofloxacin (Girgis 1999), ofloxacin (Chinh 2000; Parry 2007), and gatifloxacin (Dolecek 2008)), and ceftriaxone (Frenck 2000; Frenck 2004). Another Cochrane Review has synthesized the evidence for all fluoroquinolones for treating enteric fever (Thaver 2008). Overall, because of the small number of trials eligible for this review, pooled sample size, and wide confidence intervals for each comparison, we are not able to make firm conclusions as to the benefit of azithromycin over the other drugs. However, we have identified an ongoing trial and expect that future updates of this review will include more data and allow for further analyses (eg subgroup analysis and publication bias).

The findings of this review may not be widely generalizable for several reasons. Azithromycin was compared to few alternatives when other drugs have potential; for example, there are reports of a re-emergence of strains that are fully sensitive to first-generation antibiotics in Asia (Sood 1999; Gogia 2006). The reporting by the trials of the proportion of participants with NaR strains was poor. The response of NaR strains to antibiotics is extremely variable. Nalidixic acid-sensitive strains of *S.* Typhi and Paratyphi may not necessarily be susceptible to other fluoroquinolones. The trials all used a short-course regimen (five to seven days), which suggests a need to reduce costs and encourage adherence to treatment while ensuring effectiveness; indeed short courses have been associated with higher relapse rates in some studies of ceftriaxone (Smith 1994; Bhutta 2000). Also, all trial participants were admitted to hospital, while over 90% of people in endemic areas are treated as outpatients (Parry 2002; Bhan 2005). Two trials used ceftriaxone - this has to be administered parenterally, which means that patients have to be admitted into hospital, a practice that will increase the overall cost of treatment of the disease.

All seven trials reported on adverse events. Most adverse events were gastrointestinal in nature, and they were few and mild. Gastrointestinal bleeding occurred in one participant in each of the azithromycin and fluoroquinolone arms in Chinh 2000, and in four participants in the azithromycin arm in Dolecek 2008. Laboratory abnormalities like elevation in liver enzymes and platelet counts (thrombocytosis) were also few. Four trials compared azithromycin with fluoroquinolones, and there has been concern about the use of fluoroquinolones in children based on reports that they cause joint damage in growing beagle dogs (Burkhardt 1990; Stahlmann 2000). However, no bone, joint, or tendon abnormalities have been shown as a result of the long-term use of fluoroquinolones in other clinical conditions like cystic fibrosis and short-term use in the treatment of typhoid fever in those infected with MDR *S.* Typhi (Schaad 1995; Doherty 2000). No such adverse events were reported in the two trials comparing azithromycin with a fluoroquinolone in children and adults (Parry 2007; Dolecek 2008).

# AUTHORS' CONCLUSIONS

## Implications for practice

There is limited evidence on the superiority of azithromycin over first-line antibiotics, fluoroquinolones, and cephalosporins even when used in people infected with MDR or NaR strains of *S.* Typhi or *S.* Paratyphi, or both. Available evidence shows that azithromycin appears to be as good as the other comparator drugs for most outcomes and appears to be better than fluoroquinolones in terms of reducing clinical failure and duration of hospital stay, and ceftriaxone in terms of reducing relapse. Considering the potential of development of resistance to any new antibiotic introduced, azithromycin should be used guardedly to prevent the emergence of strains resistant to the drug.

## Implications for research

Large trials, preferably multicentred and involving outpatients in areas endemic for enteric fever should be undertaken. Also, more trials comparing azithromycin with first-line antibiotics (eg chloramphenicol, cotrimoxazole, and amoxicillin) should be undertaken as these are cheaper and have fewer reported adverse events. Furthermore, trialists should indicate clearly the proportions of participants infected with MDR and/or NaR strains of *S.* Typhi. Harmonization of the definition of outcome measures should also be done in addition to longer periods of follow up to assess long term risk of adverse events and the use of azithromycin in preventing chronic carriage of the organism. Finally, more effort should be put at standardizing use of serological tests for the rapid diagnosis of enteric fever as facilities for microbiologic isolation of the organisms are expensive and, as a result, largely unavailable in endemic areas.

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* *Indicates the major publication for the study*

# CHARACTERISTICS OF STUDIES

## Characteristics of included studies *[ordered by study ID]*

### Butler 1999

| | |
|---|---|
| Methods | Generation of allocation sequence: table of random numbers<br>Allocation concealment: sealed envelopes<br>Blinding: open<br>Inclusion of all randomized culture positive participants in final analysis: 77/92 (84%) |
| Participants | Number enrolled and randomized: 109<br>Number culture positive: 92<br>Adults aged ≥ 18 years; 26.3 years was mean age for azithromycin group and 28.5 years was mean age for chloramphenicol group<br>Inclusion criteria: fever of 38.5 °C or history of fever for 4 to 15 days; abdominal tenderness; hepatomegaly; splenomegaly; rose spots<br>Exclusion criteria: pregnancy and lactation; allergies to chloramphenicol, erythromycin, or other macrolide antibiotics; complications; prior treatment with antimicrobials within 7 days |
| Interventions | 1. Azithromycin: oral capsules at 500 mg once daily for 7 days<br>2. Chloramphenicol: oral at 2 to 3 g in 4 divided doses for 14 days |
| Outcomes | 1. Clinical failure<br>2. Bacteriological eradication<br>3. Relapse<br>4. Adverse events<br>Not included in this review<br>1. Clinical cure<br>2. Clinical improvement |
| Notes | Location: India<br>Date: not stated<br>MDR *S.* Typhi: 10 (11%) |

### Chinh 2000

| | |
|---|---|
| Methods | Generation of allocation sequence: computer-generated randomization list<br>Allocation concealment: serially numbered sealed envelopes<br>Blinding: open<br>Inclusion of all randomized culture positive participants in the final analysis: 100% |
| Participants | Number enrolled and randomized: 97<br>Number culture positive: 88<br>Adult inpatients aged ≥ 15 years with a mean age of 26.6 years in the azithromycin group and 24.7 years in the ofloxacin group<br>Inclusion criteria: clinical features of enteric fever; blood-culture positive with serovar Typhi or serovar Paratyphi A<br>Exclusion criteria: severe or complicated disease; history of significant underlying disease; history of hypersensitivity to either of the trial drug; pregnancy; previous treatment with quinolone; third-generation cephalosporin or macrolide |

**Chinh 2000** *(Continued)*

| | |
|---|---|
| | within 1 week of hospital admission |
| Interventions | 1. Azithromycin: oral 1 g daily for 5 days<br>2. Ofloxacin: oral 200 mg twice daily for 5 days |
| Outcomes | 1. Clinical failure<br>2. Microbiological failure<br>3. Relapse<br>4. Fever clearance time<br>5. Duration of hospitalization<br>6. Adverse events |
| Notes | Location: Vietnam<br>Date: not stated<br>MDR *S.* Typhi: azithromycin group 33 (77%); ofloxacin group 35 (80%) |

**Dolecek 2008**

| | |
|---|---|
| Methods | Generation of allocation sequence: computer-generated block randomization<br>Allocation concealment: sequentially numbered, folded opaque, sealed envelopes<br>Blinding: open label<br>Inclusion of all randomized culture positive participants in the final analysis: > 90% |
| Participants | Number enrolled and randomized: 358<br>Number culture positive: 287<br>Inclusion criteria: clinically suspected or culture-confirmed uncomplicated typhoid<br>Exclusion criteria: age < 6 months; history of significant underlying disease; history of hypersensitivity to either of the trial drugs; pregnancy; previous treatment with quinolone third-generation cephalosporin or macrolide within 1 week of hospital admission |
| Interventions | 1. Azithromycin: tablet or suspension 20 mg/kg/day once daily for 7 days<br>2. Gatifloxacin: oral 10 mg/kg/day once daily for 7 days |
| Outcomes | 1. Fever clearance time<br>2. Clinical failure<br>3. Microbiological failure<br>4. Relapse<br>5. Faecal carriage |
| Notes | Location: Vietnam<br>Date: 2006<br>Registration number: ISRCTN67946944<br>MDR strains: 58%<br>NaR strains: 96% |

### Frenck 2000

| | |
|---|---|
| Methods | Generation of allocation sequence: block randomization using random-number list<br>Allocation concealment: sequentially numbered sealed envelopes<br>Blinding: open label<br>Inclusion of all randomized culture positive participants in the final analysis: 100% |
| Participants | Number enrolled and randomized: 108<br>Number culture positive: 64<br>Children aged 3 to 17 years with the mean age for the azithromycin group being 9.7 years and for the ceftriaxone group 10.1 years<br>Inclusion criteria: documented fever with temperature ≥ 38.5 °C plus a history of fever for at least 4 days plus any 2 of abdominal tenderness, hepatomegaly, splenomegaly, and rose spots<br>Exclusion criteria: allergy to ceftriaxone/macrolides; major complications; significant underlying illness; treatment with *S.* Typhi susceptible antibiotics in the past 4 days; pregnancy or lactation |
| Interventions | 1. Azithromycin: oral suspension at 20 mg/kg/day with a maximum of 500 mg/day given daily for 7 days; 34 participants<br>2. Ceftriaxone: intramuscular injection at 75 mg/kg/day with a maximum of 2.5 g/day given daily for 7 days; 30 participants |
| Outcomes | 1. Clinical failure<br>2. Microbiological cure<br>3. Fever clearance<br>4. Relapse<br>5. Adverse events |
| Notes | Location: Egypt<br>Date: not reported<br>MDR *S.* Typhi: azithromycin group 5 (18%); ceftriaxone group 6 (20%) |

### Frenck 2004

| | |
|---|---|
| Methods | Generation of allocation sequence: block randomization using random-number generator<br>Allocation concealment: sequentially numbered sealed envelopes<br>Blinding: open<br>Inclusion of all randomized participants in the final analysis: 100% |
| Participants | Number enrolled and randomized: 128<br>Number analysed (culture positive): 68<br>Children and adolescent inpatients with mean age of azithromycin group being 11.8 years and ceftriaxone group being 10.8 years<br>Inclusion criteria: documented fever (rectal temperature > 38.0 °C or oral temperature > 37.5 °C) and > 2 of abdominal tenderness, hepatomegaly, splenomegaly, and/or a coated tongue<br>Exclusion criteria: allergy to both ceftriaxone and macrolides; major complications; significant underlying illness; treatment in the past 4 days with antibiotic effective against *S.* Typhi; inability to swallow oral medication |
| Interventions | 1. Azithromycin: oral suspension at 20 mg/kg/day with a maximum dose of 1000 mg/day for 5 days; 32 participants<br>2. Ceftriaxone: intravenous at 75 mg/kg/day with a maximum dose of 2.5 g/day for 5 days; 36 participants |

**Frenck 2004** *(Continued)*

| | |
|---|---|
| Outcomes | 1. Clinical failure<br>2. Microbiological failure<br>3. Clinical relapse<br>4. Duration of fever<br>5. Adverse events |
| Notes | Location: Egypt<br>Date: not reported<br>MDR *S.* Typhi: 1 participant |

### Girgis 1999

| | |
|---|---|
| Methods | Generation of allocation sequence: block randomization based on a random-number list<br>Allocation concealment: sealed envelopes<br>Blinding: participants and providers were blinded; blinding of outcome assessors unclear<br>Inclusion of all randomized culture positive participants in the final analysis: 100% |
| Participants | Number enrolled and randomized: 123<br>Number analysed (culture positive): 64<br>Adult inpatients > 18 years<br>Inclusion criteria: fever ≥ 38.5 °C plus a history of fever for at least 4 days in addition to 2 or more of abdominal tenderness, hepatomegaly, splenomegaly, and rose spots<br>Exclusion criteria: pregnancy or lactation; allergy to ciprofloxacin or erythromycin (or other macrolides); complication of typhoid fever; inability to swallow oral medication; significant underlying illness; and treatment within the past 4 days with an antibiotic potentially effective against *S.* Typhi |
| Interventions | 1. Azithromycin: oral 1 g for the first day then oral 500 mg daily for 7 days; 36 participants<br>2. Ciprofloxacin: oral 500 mg twice daily for 7 days; 28 participants |
| Outcomes | 1. Clinical failure<br>2. Microbiological failure<br>3. Relapse<br>4. Fever clearance time<br>5. Adverse events |
| Notes | Location: Egypt<br>Date: not stated<br>MDR: azithromycin group 6 (16.6%); ciprofloxacin group 15 (53.6%) |

### Parry 2007

| | |
|---|---|
| Methods | Generation of allocation sequence: computer-generated randomization list<br>Allocation concealment: serially numbered sealed envelopes<br>Inclusion of all randomized participants in final analysis: 100% |

Parry 2007 (*Continued)*

| | |
|---|---|
| Participants | Number enrolled and randomized: 241<br>Number analysed (culture positive): 199<br>Children and adults with clinical features of enteric fever<br>Inclusion criteria: documented fever for at least 4 days plus at least 1 of abdominal pain/tenderness, diarrhoea or constipation, hepatomegaly, splenomegaly, and/or rose spots<br>Exclusion criteria: evidence of severe or complicated disease; inability to swallow oral medications; history of significant underlying disease or of hypersensitivity to either of trial drugs; pregnancy or lactation; history of treatment with a fluoroquinolone or third-generation cephalosporin or macrolide within 1 week of hospital admission |
| Interventions | 1. Azithromycin: tablet or suspension 10 mg/kg/day once daily for 7 days<br>2. Ofloxacin: oral 20 mg/kg/day twice daily for 7 days |
| Outcomes | 1. Clinical failure<br>2. Microbiological failure<br>3. Relapse<br>4. Fever clearance time<br>5. Duration of hospitalization<br>6. Adverse events |
| Notes | Location of trial: Vietnam<br>Date: not stated<br>MDR strains: azithromycin group 53 (85%); ofloxacin group 57 (90%)<br>NaR strains: azithromycin group 55 (89%); ofloxacin group 62 (98%) |

MDR: multiple-drug resistant; NaR: nalidixic acid resistant.

## Characteristics of excluded studies *[ordered by study ID]*

| Study | Reason for exclusion |
|---|---|
| Chiu 1999 | Randomized controlled trial comparing azithromycin, cefixime, and no antibiotics in uncomplicated non-typhoid *Salmonella enteritis* |
| Li 2005 | Included participants with complicated typhoid fever and used intravenous azithromycin |
| Tribble 1995 | Non-comparative and non-randomized trial |
| Wallace 1994 | Report of 4 cases in which all treated with azithromycin and switched to another drug when there was no improvement |

### Characteristics of ongoing studies *[ordered by study ID]*

**ISRCTN66534807**

| | |
|---|---|
| Trial name or title | "A randomised clinical trial of Azithromycin versus Ofloxacin in the treatment of adults with uncomplicated typhoid fever at Mahosot Hospital, Vientiane, Lao People's Democratic Republic (PDR)" |
| Methods | Randomized controlled trial |
| Participants | Inclusion criteria: adult (> 15 years) non-pregnant patients with suspected or blood culture proven typhoid; fever > 37.5 °C; informed written consent to the study; able to stay in hospital for 7 days; able to take oral medication; body weight > 40 kg; likely to be able to complete 6 months' follow up; none of the exclusion criteria<br>Exclusion criteria: known hypersensitivity to ofloxacin or azithromycin; administration of chloramphenicol, co-trimoxazole, ampicillin, azithromycin, or a fluoroquinolone during the previous week; pregnancy or breastfeeding; contradictions to ofloxacin or azithromycin; evidence for severe typhoid |
| Interventions | 1. Azithromycin: oral for 3 days<br>2. Ofloxacin: oral for 3 days |
| Outcomes | 1. Fever clearance<br>2. Cure rate<br>3. Relapse rate<br>4. *S.* Typhi stool carriage rate |
| Starting date | 1 May 2004<br>Anticipated end date: 31 December 2006 |
| Contact information | Dr Paul Newton (paul@tropmedres.ac), Ministry of Health Microbiology Laboratory, Mahosot Hospital, Vientiane, Laos |
| Notes | Location: Laos<br>Registration number: ISRCTN66534807<br>Source of funding: The Wellcome Trust (UK) |

## DATA AND ANALYSES

### Comparison 1. Azithromycin (AZM) vs chloramphenicol (CM)

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Clinical failure | 1 | | Odds Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2 Microbiological failure | 1 | | Odds Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 3 Fever clearance time (hours) | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 4 Adverse events (excluding serious adverse events) | 1 | | Odds Ratio (M-H, Fixed, 95% CI) | Totals not selected |

### Comparison 2. Azithromycin (AZM) vs fluoroquinolones (FQ)

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Clinical failure | 4 | 564 | Odds Ratio (M-H, Fixed, 95% CI) | 0.48 [0.26, 0.89] |
| 2 Microbiological failure | 4 | 564 | Odds Ratio (M-H, Fixed, 95% CI) | 1.01 [0.32, 3.19] |
| 3 Relapse | 4 | 491 | Odds Ratio (M-H, Fixed, 95% CI) | 0.13 [0.01, 1.08] |
| 4 Fever clearance time (hours) | 4 | 564 | Mean Difference (IV, Random, 95% CI) | -9.80 [-34.15, 14.56] |
| 5 Duration of hospital stay (days) | 2 | 213 | Mean Difference (IV, Fixed, 95% CI) | -1.04 [-1.73, -0.34] |
| 6 Serious adverse events | 3 | | Odds Ratio (M-H, Fixed, 95% CI) | Totals not selected |

### Comparison 3. Azithromycin (AZM) vs ceftriaxone (CRO)

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Clinical failure | 2 | 132 | Odds Ratio (M-H, Fixed, 95% CI) | 2.58 [0.48, 13.87] |
| 2 Microbiological failure | 2 | 132 | Odds Ratio (M-H, Fixed, 95% CI) | 0.58 [0.07, 4.62] |
| 3 Relapse | 2 | 132 | Odds Ratio (M-H, Fixed, 95% CI) | 0.09 [0.01, 0.70] |
| 4 Fever clearance time (hours) | 2 | 132 | Mean Difference (IV, Fixed, 95% CI) | 9.12 [-1.11, 19.36] |

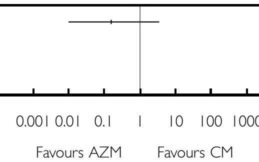
### Analysis 1.1. Comparison 1 Azithromycin (AZM) vs chloramphenicol (CM), Outcome 1 Clinical failure.

Review: Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever)

Comparison: 1 Azithromycin (AZM) vs chloramphenicol (CM)

Outcome: 1 Clinical failure

| Study or subgroup | AZM n/N | CM n/N | Odds Ratio M-H,Fixed,95% CI | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Butler 1999 | 0/42 | 2/35 | | 0.16 [ 0.01, 3.40 ] |



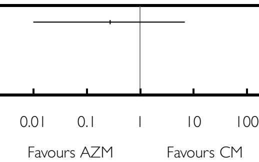

### Analysis 1.2. Comparison 1 Azithromycin (AZM) vs chloramphenicol (CM), Outcome 2 Microbiological failure.

Review: Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever)

Comparison: 1 Azithromycin (AZM) vs chloramphenicol (CM)

Outcome: 2 Microbiological failure

| Study or subgroup | AZM n/N | CM n/N | Odds Ratio M-H,Fixed,95% CI | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Butler 1999 | 0/42 | 1/35 | | 0.27 [ 0.01, 6.85 ] |



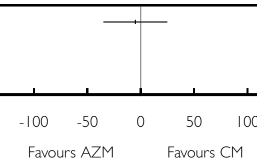
## Analysis 1.3. Comparison 1 Azithromycin (AZM) vs chloramphenicol (CM), Outcome 3 Fever clearance time (hours).

Review: Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever)

Comparison: 1 Azithromycin (AZM) vs chloramphenicol (CM)

Outcome: 3 Fever clearance time (hours)

| Study or subgroup | AZM N | AZM Mean(SD) | CM N | CM Mean(SD) | Mean Difference IV,Fixed,95% CI | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|
| Butler 1999 | 42 | 98.4 (57.6) | 35 | 103.2 (74.4) | | -4.80 [ -34.98, 25.38 ] |



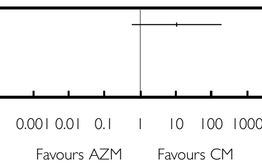

## Analysis 1.4. Comparison 1 Azithromycin (AZM) vs chloramphenicol (CM), Outcome 4 Adverse events (excluding serious adverse events).

Review: Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever)

Comparison: 1 Azithromycin (AZM) vs chloramphenicol (CM)

Outcome: 4 Adverse events (excluding serious adverse events)

| Study or subgroup | AZM n/N | CM n/N | Odds Ratio M-H,Fixed,95% CI | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Butler 1999 | 5/42 | 0/35 | | 10.41 [ 0.56, 195.25 ] |



## Analysis 2.1. Comparison 2 Azithromycin (AZM) vs fluoroquinolones (FQ), Outcome 1 Clinical failure.

Review: Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever)

Comparison: 2 Azithromycin (AZM) vs fluoroquinolones (FQ)

Outcome: 1 Clinical failure

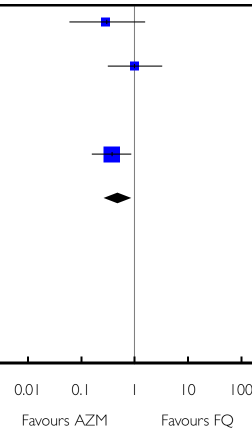
| Study or subgroup | AZM n/N | FQ n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Chinh 2000 | 2/44 | 6/44 | | 19.0 % | 0.30 [ 0.06, 1.59 ] |
| Dolecek 2008 | 6/142 | 6/145 | | 18.8 % | 1.02 [ 0.32, 3.25 ] |
| Girgis 1999 | 0/36 | 0/28 | | | Not estimable |
| Parry 2007 | 11/62 | 23/63 | | 62.2 % | 0.38 [ 0.16, 0.86 ] |
| **Total (95% CI)** | **284** | **280** | | **100.0 %** | **0.48 [ 0.26, 0.89 ]** |

Total events: 19 (AZM), 35 (FQ)

Heterogeneity: $Chi^2 = 2.28$, df = 2 (P = 0.32); $I^2 = 12\%$

Test for overall effect: Z = 2.33 (P = 0.020)

Test for subgroup differences: Not applicable



## Analysis 2.2. Comparison 2 Azithromycin (AZM) vs fluoroquinolones (FQ), Outcome 2 Microbiological failure.

Review: Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever)

Comparison: 2 Azithromycin (AZM) vs fluoroquinolones (FQ)

Outcome: 2 Microbiological failure

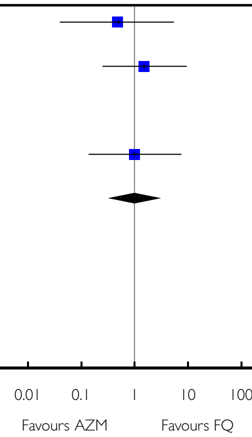
| Study or subgroup | AZM n/N | FQ n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Chinh 2000 | 1/44 | 2/44 | | 33.6 % | 0.49 [ 0.04, 5.59 ] |
| Dolecek 2008 | 3/142 | 2/145 | | 33.3 % | 1.54 [ 0.25, 9.38 ] |
| Girgis 1999 | 0/36 | 0/28 | | | Not estimable |
| Parry 2007 | 2/62 | 2/63 | | 33.0 % | 1.02 [ 0.14, 7.45 ] |
| **Total (95% CI)** | **284** | **280** | | **100.0 %** | **1.01 [ 0.32, 3.19 ]** |

Total events: 6 (AZM), 6 (FQ)

Heterogeneity: $Chi^2 = 0.55$, df = 2 (P = 0.76); $I^2 = 0.0\%$

Test for overall effect: Z = 0.02 (P = 0.98)

Test for subgroup differences: Not applicable



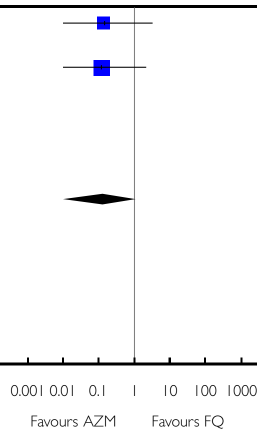
## Analysis 2.3. Comparison 2 Azithromycin (AZM) vs fluoroquinolones (FQ), Outcome 3 Relapse.

Review: Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever)

Comparison: 2 Azithromycin (AZM) vs fluoroquinolones (FQ)

Outcome: 3 Relapse

| Study or subgroup | AZM n/N | FQ n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Chinh 2000 | 0/21 | 2/17 | | 38.4 % | 0.14 [ 0.01, 3.22 ] |
| Dolecek 2008 | 0/127 | 4/137 | | 61.6 % | 0.12 [ 0.01, 2.18 ] |
| Girgis 1999 | 0/36 | 0/28 | | | Not estimable |
| Parry 2007 | 0/62 | 0/63 | | | Not estimable |
| **Total (95% CI)** | **246** | **245** | | **100.0 %** | **0.13 [ 0.01, 1.08 ]** |




Total events: 0 (AZM), 6 (FQ)

Heterogeneity: $Chi^2$ = 0.01, df = 1 (P = 0.92); $I^2$ =0.0%

Test for overall effect: Z = 1.89 (P = 0.059)

Test for subgroup differences: Not applicable

## Analysis 2.4. Comparison 2 Azithromycin (AZM) vs fluoroquinolones (FQ), Outcome 4 Fever clearance time (hours).

Review: Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever)

Comparison: 2 Azithromycin (AZM) vs fluoroquinolones (FQ)

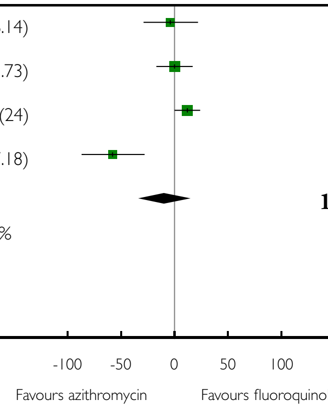
Outcome: 4 Fever clearance time (hours)

| Study or subgroup | AZM N | Mean(SD) | FQ N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Chinh 2000 | 44 | 130 (40.61) | 44 | 134 (76.14) | | 23.1 % | -4.00 [ -29.50, 21.50 ] |
| Dolecek 2008 | 142 | 106 (72.96) | 145 | 106 (73.73) | | 26.9 % | 0.0 [ -16.97, 16.97 ] |
| Girgis 1999 | 36 | 91.2 (26.4) | 28 | 79.2 (24) | | 28.6 % | 12.00 [ -0.39, 24.39 ] |
| Parry 2007 | 62 | 139.2 (67.49) | 63 | 196.8 (97.18) | | 21.4 % | -57.60 [ -86.89, -28.31 ] |
| **Total (95% CI)** | **284** | | **280** | | | **100.0 %** | **-9.80 [ -34.15, 14.56 ]** |

Heterogeneity: $Tau^2 = 499.39$; $Chi^2 = 18.55$, df = 3 (P = 0.00034); $I^2 = 84\%$

Test for overall effect: Z = 0.79 (P = 0.43)

Test for subgroup differences: Not applicable



## Analysis 2.5. Comparison 2 Azithromycin (AZM) vs fluoroquinolones (FQ), Outcome 5 Duration of hospital stay (days).

Review: Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever)

Comparison: 2 Azithromycin (AZM) vs fluoroquinolones (FQ)

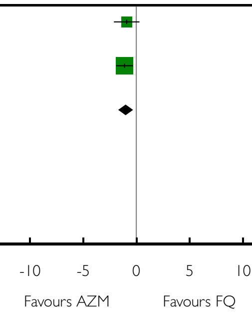
Outcome: 5 Duration of hospital stay (days)

| Study or subgroup | AZM | | FQ | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Chinh 2000 | 44 | 9.6 (2.37) | 44 | 10.5 (3.38) | | 32.4 % | -0.90 [ -2.12, 0.32 ] |
| Parry 2007 | 62 | 12.6 (2.2) | 63 | 13.7 (2.6) | | 67.6 % | -1.10 [ -1.94, -0.26 ] |
| **Total (95% CI)** | **106** | | **107** | | | **100.0 %** | **-1.04 [ -1.73, -0.34 ]** |

Heterogeneity: Chi$^2$ = 0.07, df = 1 (P = 0.79); I$^2$ =0.0%

Test for overall effect: Z = 2.92 (P = 0.0035)

Test for subgroup differences: Not applicable



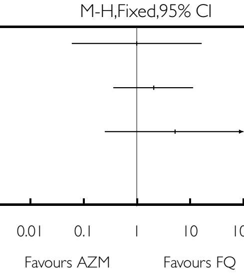

## Analysis 2.6. Comparison 2 Azithromycin (AZM) vs fluoroquinolones (FQ), Outcome 6 Serious adverse events.

Review: Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever)

Comparison: 2 Azithromycin (AZM) vs fluoroquinolones (FQ)

Outcome: 6 Serious adverse events

| Study or subgroup | AZM | FQ | Odds Ratio | Odds Ratio |
|---|---|---|---|---|
| | n/N | n/N | M-H,Fixed,95% CI | M-H,Fixed,95% CI |
| Chinh 2000 | 1/44 | 1/44 | | 1.00 [ 0.06, 16.51 ] |
| Dolecek 2008 | 4/142 | 2/145 | | 2.07 [ 0.37, 11.50 ] |
| Parry 2007 | 2/62 | 0/63 | | 5.25 [ 0.25, 111.56 ] |



## Analysis 3.1. Comparison 3 Azithromycin (AZM) vs ceftriaxone (CRO), Outcome 1 Clinical failure.

Review: Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever)

Comparison: 3 Azithromycin (AZM) vs ceftriaxone (CRO)

Outcome: 1 Clinical failure

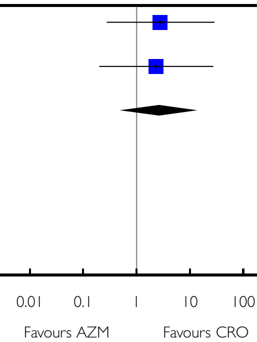
| Study or subgroup | AZM n/N | CRO n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Frenck 2000 | 3/34 | 1/30 | | 52.3 % | 2.81 [ 0.28, 28.53 ] |
| Frenck 2004 | 2/32 | 1/36 | | 47.7 % | 2.33 [ 0.20, 27.03 ] |
| **Total (95% CI)** | **66** | **66** | | **100.0 %** | **2.58 [ 0.48, 13.87 ]** |

Total events: 5 (AZM), 2 (CRO)

Heterogeneity: $Chi^2 = 0.01$, df = 1 (P = 0.91); $I^2 = 0.0\%$

Test for overall effect: Z = 1.10 (P = 0.27)

Test for subgroup differences: Not applicable




## Analysis 3.2. Comparison 3 Azithromycin (AZM) vs ceftriaxone (CRO), Outcome 2 Microbiological failure.

Review: Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever)

Comparison: 3 Azithromycin (AZM) vs ceftriaxone (CRO)

Outcome: 2 Microbiological failure

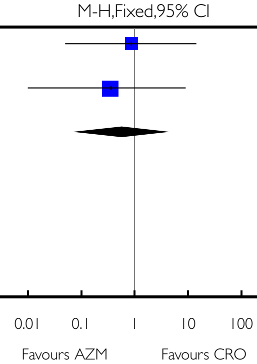
| Study or subgroup | AZM n/N | CRO n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Frenck 2000 | 1/34 | 1/30 | | 42.5 % | 0.88 [ 0.05, 14.69 ] |
| Frenck 2004 | 0/32 | 1/36 | | 57.5 % | 0.36 [ 0.01, 9.26 ] |
| **Total (95% CI)** | **66** | **66** | | **100.0 %** | **0.58 [ 0.07, 4.62 ]** |

Total events: 1 (AZM), 2 (CRO)

Heterogeneity: $Chi^2 = 0.16$, df = 1 (P = 0.69); $I^2 = 0.0\%$

Test for overall effect: Z = 0.51 (P = 0.61)

Test for subgroup differences: Not applicable



## Analysis 3.3. Comparison 3 Azithromycin (AZM) vs ceftriaxone (CRO), Outcome 3 Relapse.

Review: Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever)

Comparison: 3 Azithromycin (AZM) vs ceftriaxone (CRO)

Outcome: 3 Relapse

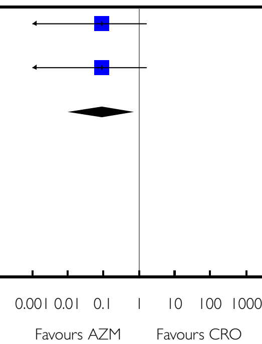
| Study or subgroup | AZM n/N | CRO n/N | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Frenck 2000 | 0/34 | 4/30 | 47.9 % | 0.09 [ 0.00, 1.66 ] |
| Frenck 2004 | 0/32 | 5/36 | 52.1 % | 0.09 [ 0.00, 1.66 ] |
| **Total (95% CI)** | **66** | **66** | **100.0 %** | **0.09 [ 0.01, 0.70 ]** |

Total events: 0 (AZM), 9 (CRO)

Heterogeneity: Chi$^2$ = 0.00, df = 1 (P = 0.99); I$^2$ =0.0%

Test for overall effect: Z = 2.29 (P = 0.022)

Test for subgroup differences: Not applicable




## Analysis 3.4. Comparison 3 Azithromycin (AZM) vs ceftriaxone (CRO), Outcome 4 Fever clearance time (hours).

Review: Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever)

Comparison: 3 Azithromycin (AZM) vs ceftriaxone (CRO)

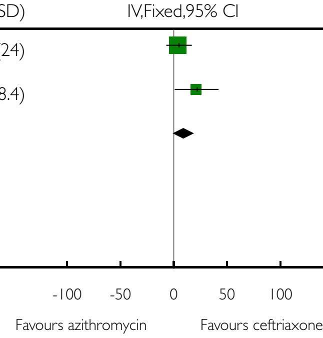
Outcome: 4 Fever clearance time (hours)

| Study or subgroup | AZM N | AZM Mean(SD) | CRO N | CRO Mean(SD) | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|
| Frenck 2000 | 34 | 98.4 (24.4) | 30 | 93.6 (24) | 74.3 % | 4.80 [ -7.08, 16.68 ] |
| Frenck 2004 | 32 | 108 (45.6) | 36 | 86.4 (38.4) | 25.7 % | 21.60 [ 1.43, 41.77 ] |
| **Total (95% CI)** | **66** | | **66** | | **100.0 %** | **9.12 [ -1.11, 19.36 ]** |

Heterogeneity: Chi$^2$ = 1.98, df = 1 (P = 0.16); I$^2$ =49%

Test for overall effect: Z = 1.75 (P = 0.081)

Test for subgroup differences: Not applicable



## ADDITIONAL TABLES

**Table 1. Detailed search strategies**

| Search set | CIDG SR[a] | CENTRAL | MEDLINE[b] | EMBASE[b] | LILACS[b] |
|---|---|---|---|---|---|
| 1 | azithromycin | azithromycin | azithromycin | azithromycin | azithromycin |
| 2 | typhoid fever* | typhoid fever* | typhoid fever* | typhoid fever* | typhoid fever* |
| 3 | paratyphoid fever* | paratyphoid fever* | paratyphoid fever* | paratyphoid fever$ | paratyphoid* |
| 4 | salmonell* | enteric fever | enteric fever | enteric fever | salmonell* |
| 5 | 2 or 3 or 4 | TYPHOID FEVER | TYPHOID FEVER | TYPHOID FEVER | 2 or 3 or 4 |
| 6 | 1 and 5 | SALMONELL* | PARATYPHOID FEVER | salmonell$ | 1 and 5 |
| 7 | - | 2 or 3 or 4 or 5 or 6 | salmonell* | 2 or 3 or 4 or 5 or 6 | - |
| 8 | - | 1 and 7 | 2 or 3 or 4 or 5 or 6 or 7 | 1 and 7 | - |
| 9 | - | - | 1 and 8 | Limit 8 to humans | - |
| 10 | - | - | Limit 9 to humans | - | - |

[a]Cochrane Infectious Diseases Group Specialized Register.
[b]Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Lefebvre 2008); upper case: MeSH or EMTREE heading; lower case: free text term.

**Table 2. Definitions of outcome measures**

| Comparison | Trial | Clinical failure | Microbiological failure | Relapse | Fever clearance time |
|---|---|---|---|---|---|
| Azithromycin vs chloramphenicol | Butler 1999 | Lack of improvement or worsening of signs and symptoms or need to change antibiotic therapy | Not defined | Clinical: return of fever after day 14<br>Bacteriological recurrence: blood culture positive for *S.* Typhi or *S.* Paratyphi on day 21 or 35 days after start of therapy | Not defined |
| Azithromycin vs fluoroquinolones | Girgis 1999 | Lack of resolution of symptoms by day 7 or development of a major complication of typhoid fever after 5 | Blood culture positive for *S.* Typhi or *S.* Paratyphi on day 4 or 10 | Recurrence of fever with signs and symptoms of typhoid fever within 4 weeks of therapy completion | First day on which maximum temperature < 38.0 °C with maintenance of tem- |

**Table 2. Definitions of outcome measures** *(Continued)*

| | | | | | |
|---|---|---|---|---|---|
| | | days of therapy | | along with isolation of organism in culture | perature at this level for at least 48 hours |
| | Chinh 2000 | Persistence of fever and symptoms for > 5 days after end of treatment or development of severe complications during treatment, requiring a change in therapy | Isolation of *S.* Typhi or serovar *S.* Paratyphi A from blood or a sterile site after completion of treatment | Recurrence of symptoms and signs suggestive of enteric fever after the participant had been discharged as well from the hospital | Time from start of treatment until the body temperature fell < 37.5 °C and remained at < 37.5 °C for 48 hours |
| | Parry 2007 | Persistence of fever and at least 1 other typhoid related symptom for > 7 days after start of treatment, or development of complications during treatment requiring change in therapy | Isolation of *S.* Typhi or Paratyphi from blood or sterile site after completion of treatment | Recurrence of symptoms and signs suggestive of enteric fever within the 4-week period after participant discharged from hospital plus blood culture positive for *S.* Typhi or *S.* Paratyphi | Time from start of treatment until body temperature 37.5 °C and remained so for 48 hours |
| | Dolecek 2008 | Persistence of fever and symptoms 2 days after end of treatment, ie on day 10 or need for re-treatment due to insufficient treatment response as judged by the treating physician | Positive blood culture on day 7 to 9 after start of treatment | Occurrence of symptoms and signs of typhoid fever within 1 month after completion of treatment | Time from the start of the antibiotic treatment to when the axillary temperature first fell ≤ 37.5 °C and remained there for at least 48 hours |
| Azithromycin vs ceftriaxone | Frenck 2000 | Persistence of > 1 typhoid-related symptom or sign present at study entry, or development of a typhoid-related complication after at least 4 days of therapy | Not defined | Recurrence of fever with symptoms of typhoid fever within 4 weeks of completion of therapy along with isolation of *S.* Typhi or *S.* Paratyphi from blood | Not defined |
| | Frenck 2004 | Persistence of > 2 typhoid-related symptoms or signs present at study entry or as development of a typhoid-related com- | Blood culture positive for *S.* Typhi on day 8 | Recurrence of fever and clinical features of typhoid within 30 days of completing therapy, along with isolation of *S.* Typhi | Not defined |

**Table 2. Definitions of outcome measures** *(Continued)*

| | | | | | |
|---|---|---|---|---|---|
| | | plication | | from the blood | |

*S.* Paratyphi: *Salmonella enterica* serovar Paratyphi; *S.* Typhi: *Salmonella enterica* serovar Typhi.

**Table 3. Participants with MDR and NaR strains**

| Comparison | Trial | Participants | Culture positive (site) | S. Typhi/ Paratyphi | Number (%) with MDR | Number (%) with NaR | Notes |
|---|---|---|---|---|---|---|---|
| Azithromycin vs chloramphenicol | Butler 1999 | 109 enrolled and randomized | 92 (blood) | 82/10 azithromycin<br>38/4 chloramphenicol<br>29/6 15 participants excluded for various reasons | 10 (11%) | Not stated | - |
| Azithromycin vs fluoroquinolone | Chinh 2000 | 97 enrolled and randomized | 88 (blood) | 86/2 not stated | 68 (77.2%)<br>Azithromycin: 33<br>Fluoroquinolone 35 | 46 (52%)<br>Azithromycin: 25<br>Fluoroquinolon: 21 | 1 isolate was not available for sensitivity testing |
| | Girgis 1999 | 123 enrolled and randomized | 52 (blood) ; 2 (stool); 10 (both blood and stool) | 34/2 azithromycin<br>26/2 ciprofloxacin | 21 (33%)<br>Azithromycin: 6<br>Fluoroquinolone: 15 | Not stated | - |
| | Parry 2007 | 241 enrolled and randomized | 199 (blood or bone marrow) | 198/1<br>62/0 azithromycin<br>63/0 ofloxacin<br>62/1 ofloxacin-azithromycin | 165 (83%)<br>Azithromycin: 53<br>Fluoroquinolone: 57 | 172 (86%)<br>Azithromycin 55 (89%)<br>Fluoroquinolone 62 (98%) | This study had 3 arms |
| | Dolecek 2008 | 358 enrolled and randomized | 288 (blood or bone marrow) | 144/1 gatifloxacin<br>138/4 azithromycin | 153 (58%)<br>Gatifloxacin: 87 (63.5%)<br>Azithromycin: 66 (52.3%) | 254 (96.5%)<br>Gatifloxacin: 132 (96.3%)<br>Azithromycin: 121 (96%) | Only 263 isolates had antibiotic susceptibility testing |
| Azithromycin vs ceftriaxone | Frenck 2000 | 108 enrolled and randomized | 64 (blood) | 64/0 | 11 (17.2%) | Not stated | - |

**Table 3. Participants with MDR and NaR strains** *(Continued)*

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Frenck 2004 | 128 enrolled and randomized | 65 (blood); 13 (stool) | 64/0 | 1 (1.5%) | Not stated | - |

MDR: multiple-drug resistant; NaR: nalidixic acid resistant.

**Table 4. Risk of bias assessment**

| Comparison | Trial | Allocation sequence generation | Allocation concealment | Blinding | Randomized participants in the analysis |
|---|---|---|---|---|---|
| Azithromycin vs chloramphenicol | Butler 1999 | Adequate | Adequate | Open | Inadequate |
| Azithromycin vs ofloxacin | Chinh 2000 | Adequate | Adequate | Open | Adequate |
| Azithromycin vs gatifloxacin | Dolecek 2008 | Adequate | Adequate | Open | Adequate |
| Azithromycin vs ciprofloxacin | Girgis 1999 | Adequate | Adequate | Open | Adequate |
| Azithromycin vs ofloxacin | Parry 2007 | Adequate | Adequate | Open | Adequate |
| Azithromycin vs ceftriaxone | Frenck 2000 | Adequate | Adequate | Open | Adequate |
| Azithromycin vs ceftriaxone | Frenck 2004 | Adequate | Adequate | Open | Adequate |

**Table 5. Serious adverse events**

| Comparison | Trial | Intervention | Control |
|---|---|---|---|
| Azithromycin vs chloramphenicol | Butler 1999 | None | None |
| Azithromycin vs fluoroquinolone | Chinh 2000 | None | None |
| | Dolecek 2008 | None | None |
| | Girgis 1999 | None | None |
| | Parry 2007 | None | None |

**Table 5. Serious adverse events** *(Continued)*

| | | | |
|---|---|---|---|
| Azithromycin vs ceftriaxone | Frenck 2000 | None | None |
| | Frenck 2004 | None | None |

**Table 6. Other adverse events**

| Comparison | Trial | Clinical adverse events[a] | | Laboratory adverse events[a] | |
|---|---|---|---|---|---|
| | | Intervention | Control | Intervention | Control |
| Azithromycin vs chloramphenicol | Butler 1999 | Azithromycin: 5 gastrointestinal (2) others not stated | None | Not described | Not described |
| Azithromycin vs fluoroquinolone | Chinh 2000 | Azithromycin: Gastrointestinal bleeding (1); nausea (5); vomiting (5) ; abdominal pain (4); skin rash (1) | Ofloxacin Gastrointestinal bleeding; nausea (1); vomiting (3); abdominal pain (4); skin rash (0) | Azithromycin: mild elevation in mean transaminase levels | Ofloxacin: mild elevation in mean transaminase levels |
| | Girgis 1999 | Azithromycin: nausea or vomiting (6) ; lightheadedness (2) ; dry throat or mouth (3); loose stools (3); constipation (2) | Ciprofloxacin: nausea or vomiting (4) ; lightheadedness (2) ; dry throat or mouth (4); loose stools (3); constipation (2) | Azithromycin: thrombocytosis (4); mild increase in aspartate amino transaminase levels (2) | Ciprofloxacin: thrombocytosis (1); mild increases in aspartate transaminases levels (3) |
| | Parry 2007 | Azithromycin: joint discomfort (1) | Ofloxacin: joint discomfort | Azithromycin: none | Ofloxacin: none |
| | Dolecek 2008 | Azithromycin: Gastrointestinal bleeding (4)<br>Liver dysfunction (2)<br>Maculopapular rash (1)<br>Pneumonia (2) | Gatifloxacin: vomiting (1); diarrhoea (1) | Azithromycin: mild elevations in median transaminase levels | Gatifloxacin: mild elevations in median transaminase levels |
| Azithromycin vs ceftriaxone | Frenck 2000 | Azithromycin: gastrointestinal symptoms most commonly vomiting | Ceftriaxone: gastrointestinal symptom less; pains at injection site (6) | Azithromycin: mild elevation in alanine aminotransferase (1) and aspartate transaminases (2) ; thrombocytosis (4) | Ceftriaxone: mild elevations in alanine transaminase (1) and aspartate transaminase (4), thrombocytosis (3) |
| | Frenck 2004 | Azithromycin: vomiting (11); diar- | Ceftriaxone: vomiting (7); diar- | Azithromycin: mild increases | Ceftriaxone: mild increases |

**Table 6. Other adverse events** *(Continued)*

| | | | | | |
|---|---|---|---|---|---|
| | | rhoea (10); nausea (5) ; abdominal pain (3) ; anorexia (3); cough (3) | rhoea (15); nausea (7) ; abdominal pain (5) ; anorexia (6); cough (2) | in aspartate transaminase levels (2) and alanine transaminase levels (2); thrombocytosis (7) | in aspartate transaminase levels (2) and alanine transaminase levels (5); thrombocytosis (7) |

[a]Number of participants with adverse event.

# WHAT'S NEW

| Date | Event | Description |
|---|---|---|
| 2 September 2011 | Amended | Azithromycin treatments are included in another Cochrane review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever). This latter review is in the process of being updated, and this review on azithromycin is therefore withdrawn<br>The CIDG is piloting a new classification system for reviews. The classification for this has now been added; description included in "Published notes" section of review |

# CONTRIBUTIONS OF AUTHORS

Emmanuel Effa wrote the protocol, assisted in conducting the literature search, extracted data, and wrote the review. Hasifa Bukirwa co-extracted data and provided guidance, editorial support, and mentoring.

# DECLARATIONS OF INTEREST

None known.


# SOURCES OF SUPPORT

## Internal sources

- University of Calabar Teaching Hospital, Nigeria.
- Effective Health Care Alliance Programme (EHCAP), Nigeria.

## External sources

- Reviews for Africa Programme Fellowship, South Africa.
- Department for International Development (DFID), UK.

# DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We attempted to search according to the methods outlined in the protocol; we were unable to retrieve some conference proceedings or obtain information on studies from some organizations and pharmaceutical companies contacted. Data were extracted as specified in the trial protocol.

# NOTES

2011, Issue 10: Review status: Current question - no update intended. Azithromycin treatments are included in the review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever). (Thaver D, Zaidi AKM, Critchley JA, Azmatullah A, Madni SA, Bhutta ZA. Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever). Cochrane Database of Systematic Reviews 2008, Issue 4. Art. No.: CD004530. DOI: 10.1002/14651858.CD004530.pub3.) This latter review is being updated, and will be published in late 2011. The azithrocycin review is therefore withdrawn.

The review status reports aims to help the reader understand whether the review concerns a current question, and whether it is up to date. It is a pilot project by the Cochrane Infectious Diseases Group editors to help readers and we welcome feedback. It has three components:

**1. Whether the review is currently relevan**t. For this, we classify reviews into:

- Historical question, where the intervention or policy has been superseded by new medical developments (such as a new drug);
- Current question, which is still relevant to current policy or practice.

**2. Whether the review is up to date**: for this, we classify reviews into:

- Up to date;
- Update pending; or
- No update intended.

**3. An explanation of the review status.**

This narrative text provides a little more additional information to explain the categories selected.

# INDEX TERMS

## Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*therapeutic use]; Azithromycin [*therapeutic use]; Paratyphoid Fever [*drug therapy]; Randomized Controlled Trials as Topic; Typhoid Fever [*drug therapy]

## MeSH check words

Adolescent; Adult; Child; Humans